

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

| | |
|----------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Date of mailing (day/month/year) 19 May 1999 (19.05.99) | To: United States Patent and Trademark Office (Box PCT) Crystal Plaza 2 Washington, DC 20231 ÉTATS-UNIS D'AMÉRIQUE in its capacity as elected Office |
| International application No. PCT/GB98/02867 | Applicant's or agent's file reference P4644.WOCTH |
| International filing date (day/month/year) 23 September 1998 (23.09.98) | Priority date (day/month/year) 25 September 1997 (25.09.97) |
| Applicant BEBBINGTON, Chris et al | |

1. The designated Office is hereby notified of its election made:

in the demand filed with the International Preliminary Examining Authority on:

09 April 1999 (09.04.99)

in a notice effecting later election filed with the International Bureau on:

2. The election was

was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

| | |
|---------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|
| The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35 | Authorized officer Lazar Joseph Panakal Telephone No.: (41-22) 338.83.38 |
|---------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|

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PENT COOPERATION TREATY

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INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

| | | |
|-------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------|
| Applicant's or agent's file reference P4644.WOCTH | FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below. | |
| International application No. PCT/GB 98/ 02867 | International filing date (day/month/year) 23/09/1998 | (Earliest) Priority Date (day/month/year) 25/09/1997 |
| Applicant OXFORD BIOMEDICA (UK) LIMITED et al. | | |

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

It is also accompanied by a copy of each prior art document cited in this report.

1. Certain claims were found unsearchable (see Box I).
2. Unity of invention is lacking (see Box II).
3. The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing
 - filed with the international application.
 - furnished by the applicant separately from the international application,
 - but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
 - Transcribed by this Authority

4. With regard to the title,
 - the text is approved as submitted by the applicant
 - the text has been established by this Authority to read as follows:

RETROVIRAL VECTORS COMPRISING A FUNCTIONAL SPLICE DONOR SITE AND A FUNCTIONAL SPLICE ACCEPTOR SITE

5. With regard to the abstract,
 - the text is approved as submitted by the applicant
 - the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is:

Figure No. _____

- as suggested by the applicant.
- because the applicant failed to suggest a figure.
- because this figure better characterizes the invention.

None of the figures.

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 98/02867

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 6 C12N15/86 C12N7/01 C12N5/10 C12N15/63 C12N15/53
 A61K48/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC 6 C12N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|----------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------|
| Y | WO 94 29470 A (MASSACHUSETTS INST TECHNOLOGY) 22 December 1994 see page 13, line 25 - line 32; figure 1 --- | 1-14, 18-28, 30,37,42 |
| Y | ✓MORGENSTERN J. P. ET AL: "ADVANCED MAMMALIAN GENE TRANSFER: HIGH TITRE RETROVIRAL VECTORS WITH MULTIPLE DRUG SELECTION MARKERS AND A COMPLEMENTARY HELPER-FREE PACKAGING CELL LINE" NUCLEIC ACIDS RESEARCH, vol. 18, no. 12, 1990, pages 3587-3596, XP002073969 see the whole document --- | 1-14, 18-28, 30,37,42 |

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

° Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

27 January 1999

09/02/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patenttaan 2
 NL - 2280 HV Rijswijk
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 Fax: (+31-70) 340-3016

Authorized officer

Mand1, B

INTERNATIONAL SEARCH REPORT

Inte
onal Application No

PCT/GB 98/02867

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|----------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------|
| X | ✓WO 96 28563 A (BAVARIAN NORDIC ;GSF FORSCHUNGSZENTRUM UMWELT (DE); GUENZBURG WALT) 19 September 1996 see page 8, last paragraph - page 9, last paragraph --- | 32,37 |
| X | ✓BILBAO G. ET AL.: "Adenoviral/retroviral vector chimeras: a novel strategy to achieve high-efficiency stable transduction in vivo." THE FASEB JOURNAL, vol. 11, 11 July 1997, pages 624-634, XP002091318 see the whole document --- | 33,34, 36,38,40 |
| X | ✓PROMEGA PRODUCT CATALOG 1997; XP002091320 see page 254 - page 255 --- | 39 |
| A | ✓ZHENG B. ET AL.: "Increment of hFIX expression with endogenous intron 1 in vitro." CELL RESEARCH, vol. 7, no. 1, June 1997, pages 21-29, XP002091319 see the whole document ----- | 15-18 |
| A | ✓ | 31 |
| P,X | ✓WO 98 15636 A (GAROFF HENRIK ;LI KEJUN (SE)) 16 April 1998 see the whole document ----- | 1-14, 18-28, 30,37,42 |
| | | 33,40 |

INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB 98/02867

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.:

because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 28 and 31, as far as an in vivo application is concerned, are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. Claims Nos.:

because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. Claims Nos.:

because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-28,30,42

A retroviral vector comprising splice donor and acceptors sites that can only function in transduced cells; a cell transfected or transduced with said vector; and a method for transfecting said cell.

2. Claims: 29,33-36,40,41

A delivery system for a retroviral vector.

3. Claim : 31

Use of a functional intron to restrict expression of a nucleic acid sequence within a desired target cell.

4. Claim : 32

Use of reverse transcriptase to deliver a first nucleotide sequence from the 3'-end of a retroviral pro-vector to the 5'-end of a retroviral vector.

5. Claim : 37

A lentiviral vector system.

6. Claim : 38

An adenoviral vector system.

7. Claim : 39

Vectors or plasmids based on or obtained from any one or more entities presented as in pElsp1A, pCI-Neo, pElRevE, pElHORSE3.1, pElPEGASUS4, pCI-Rab, pElRab.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 98/02867

| Patent document cited in search report | Publication date | Patent family member(s) | | Publication date |
|----------------------------------------|------------------|-------------------------|-----------|------------------|
| WO 9429470 A | 22-12-1994 | US | 5631162 A | 20-05-1997 |
| | | CA | 2164953 A | 22-12-1994 |
| | | EP | 0706575 A | 17-04-1996 |
| | | JP | 9501046 T | 04-02-1997 |
| WO 9628563 A | 19-09-1996 | AU | 5103996 A | 02-10-1996 |
| | | EP | 0817858 A | 14-01-1998 |
| WO 9815636 A | 16-04-1998 | AU | 4642297 A | 05-05-1998 |

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB 98/02867

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 28 and 31, as far as an *in vivo* application is concerned, are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

nce withinnational Searching Authority found multiple (groups of) inventions in this inernational application, as follows:

1. Claims: 1-28,30,42

A retroviral vector comprising splice donor and acceptors sites that can only function in transduced cells; a cell tranfected or transduced with said vector; and a method for tranfecting said cell.

2. Claims: 29,33-36,40,41

A delivery system for a retroviral vector.

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5. Claim : 37

A lentiviral vector system.

6. Claim : 38

An adenoviral vector system.

7. Claim : 39

Vectors or plasmids based on or obtained from any one or more entities presented as in pE1splA, pCI-Neo, pE1RevE, pE1HORSE3.1, PE1PEGASUS4, pCI-Rab, pE1Rab.

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PATENT COOPERATION TREATY

REC'D 11 JAN 2000

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WIPO PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

| | | |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------|-----------------------------------------------------------------------------------------------------|
| Applicant's or agent's file reference P004644WOCTH | FOR FURTHER ACTION | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
| International application No. PCT/GB98/02867 | International filing date (day/month/year) 23/09/1998 | Priority date (day/month/year) 25/09/1997 |
| International Patent Classification (IPC) or national classification and IPC C12N15/86 | | |
| Applicant OXFORD BIOMEDICA (UK) LIMITED et al. | | |
| <p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 6 sheets, including this cover sheet.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of sheets.</p> | | |
| <p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> I <input checked="" type="checkbox"/> Basis of the report II <input type="checkbox"/> Priority III <input type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV <input type="checkbox"/> Lack of unity of invention V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI <input checked="" type="checkbox"/> Certain documents cited VII <input type="checkbox"/> Certain defects in the international application VIII <input checked="" type="checkbox"/> Certain observations on the international application | | |

| | |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|
| Date of submission of the demand 09/04/1999 | Date of completion of this report 05.01.00 |
| Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465 | Authorized officer Roscoe, R Telephone No. +49 89 2399 2554 |



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**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB98/02867

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-91 as originally filed

Claims, No.:

1-42 as originally filed

Drawings, sheets:

1/34-34/34 as originally filed

2. The amendments have resulted in the cancellation of:

the description, pages:
 the claims, Nos.:
 the drawings, sheets:

3. This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

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**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB98/02867

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

| | | |
|-------------------------------|------|--------------------|
| Novelty (N) | Yes: | Claims 1-30, 41 |
| | No: | Claims 31-40, 42 |
| Inventive step (IS) | Yes: | Claims 1-30, 41 |
| | No: | Claims 31-40, 42 |
| Industrial applicability (IA) | Yes: | Claims 1-27, 29-42 |
| | No: | Claims 28 |

2. Citations and explanations

see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

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1. Citations

The documents mentioned in the present International Preliminary Examination Report are numbered as in the search report, i.e. D1 corresponds to the first document of the search report etc.

**2. Reasoned statement on Novelty, Inventive Step and Industrial Applicability
(Section V)**

2.1 Novelty (Art.33(2) PCT)

Claim 31 lacks novelty over the insertion of Intron 1 into FIX cDNA in D6. Here the intron has regulatory functions which may be partially cell-type specific and thus restrictive. (the claim is so broad anyway that it could not be considered anything but trivial if the non-novel subject-matter were excluded).

Claim 32 lacks novelty over D3 where reverse transcriptase delivers a promoter from the 3' to the 5' end of a retroviral vector.

Claims 33-38 and 40 lack novelty over the hybrid viral vector systems of D4. These systems basically employ two "adenovirally packed constructs", one of which comprises a complete recombinant retroviral genome (MLV is used to demonstrate the system, however it is considered applicable to all retroviruses). After infection of a first target cell, recombinant retrovirus is produced which is capable of transducing a second target cell. The split-intron configuration in claims 35-38 could not be taken into account in the assessment of these claims since it is unclear.

Claim 39 cannot be considered novel over D5, since pCI can presumably be obtained from pCI-Neo.

Claim 42 is basically not novel because other claims are not novel.

2.2 Inventive Step (Art.33(3) PCT)

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The cited prior art neither discloses nor suggests developing a retroviral vector system in which splicing of pro-vector and vector differ due to the use of the mechanism of retroviral reverse transcription to modify relative positions of splice sites. D2 discloses splice site inactivation by point mutation but splicing pattern is retained in both pro-vector and vector. The splice site is not mobile and the splicing is not employed as a regulatory switch. In D3, splicing is again not used as a regulatory switch, but the paper demonstrates how the position of a regulatory element (in this case a promoter) can be switched by the reverse transcription process. Nevertheless, no mention of moving a splice site or other regulatory elements is made in D3. Hence, these documents do not lead the skilled person to the present invention.

Not all claims are restricted to subject-matter which falls within the scope of the above - see section 2.1 (these claims are presently considered to lack novelty but would be considered non-inventive should the novelty-lacking subject-matter be removed without introducing the essential technical features of the above-acknowledged invention.

2.3 Industrial Applicability (Art.33(4) PCT)

For the assessment of the present claim 28 on the question whether it is industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

3. Certain documents (Section VI)

In accordance with Rule 70.10, PCT, applicants attention is drawn to the following document(s):

WO-A-98/15636 (Publication date, 16.04.98; Priority dates, 10.10.96 / 03.07.97;
Filing date, 10.10.97)

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**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB98/02867

4. Certain observations (Section VIII)

4.1 Clarity (Art.6 PCT)

Claim 2 seems pointless since a nucleotide sequence that yields a non-functional splice donor site is undefined - it can be basically anything apart from a functional splice site.

The dependency of claim 30 is inappropriate since some of the preceding claims do not relate to retroviral provectors.

The terminology "restrict expression" in claim 31 is unclear.

The terminology "split-intron configuration" is considered technically unclear.
Hence, claims 35-38 are unclear.

The vectors claimed in claim 39 appear to be defined by arbitrary nomenclature.
Products must be defined by technical features. + spelling "basd"

Claims which are not for defined subject-matter are unallowable. Hence, claim 42 needs to be deleted.

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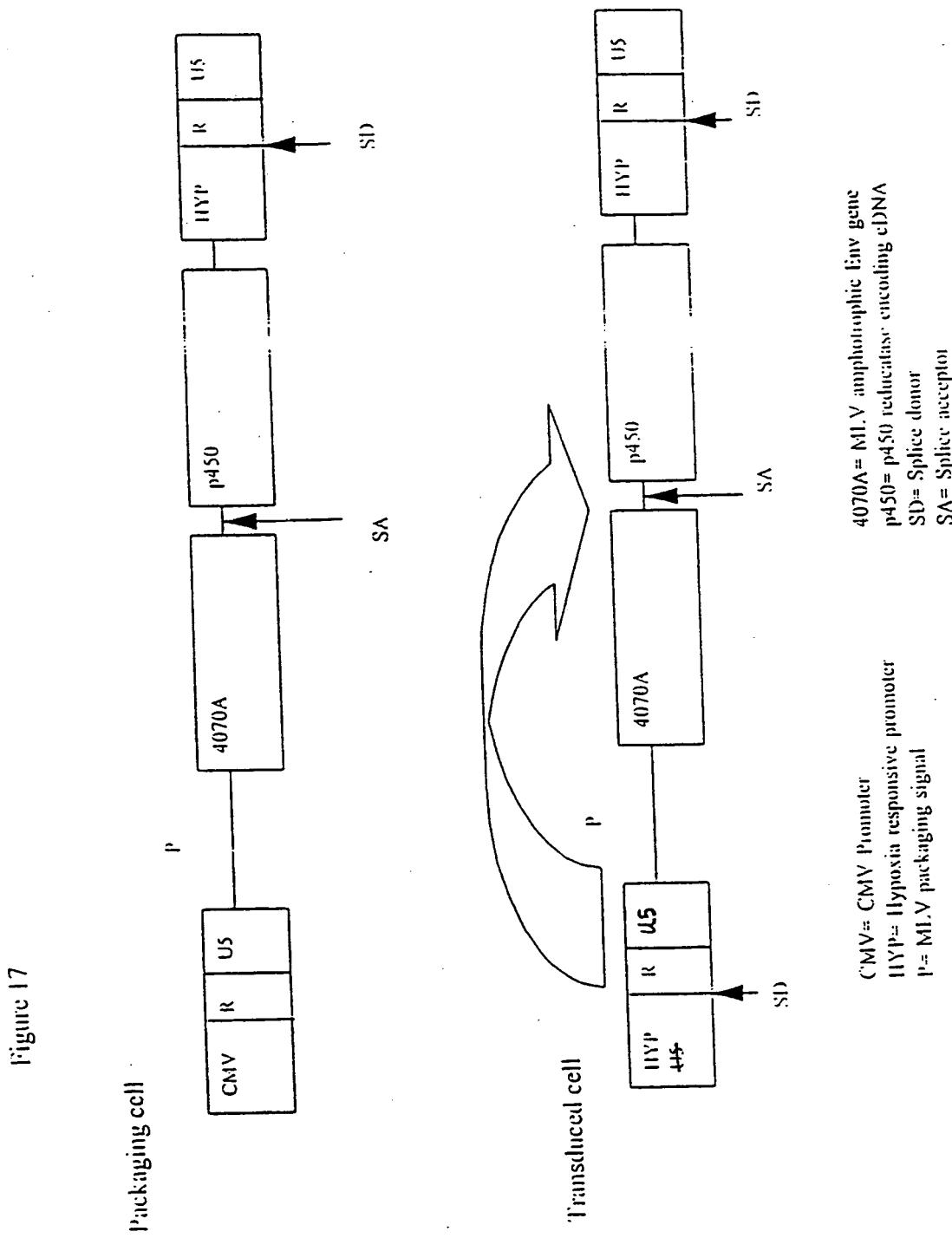
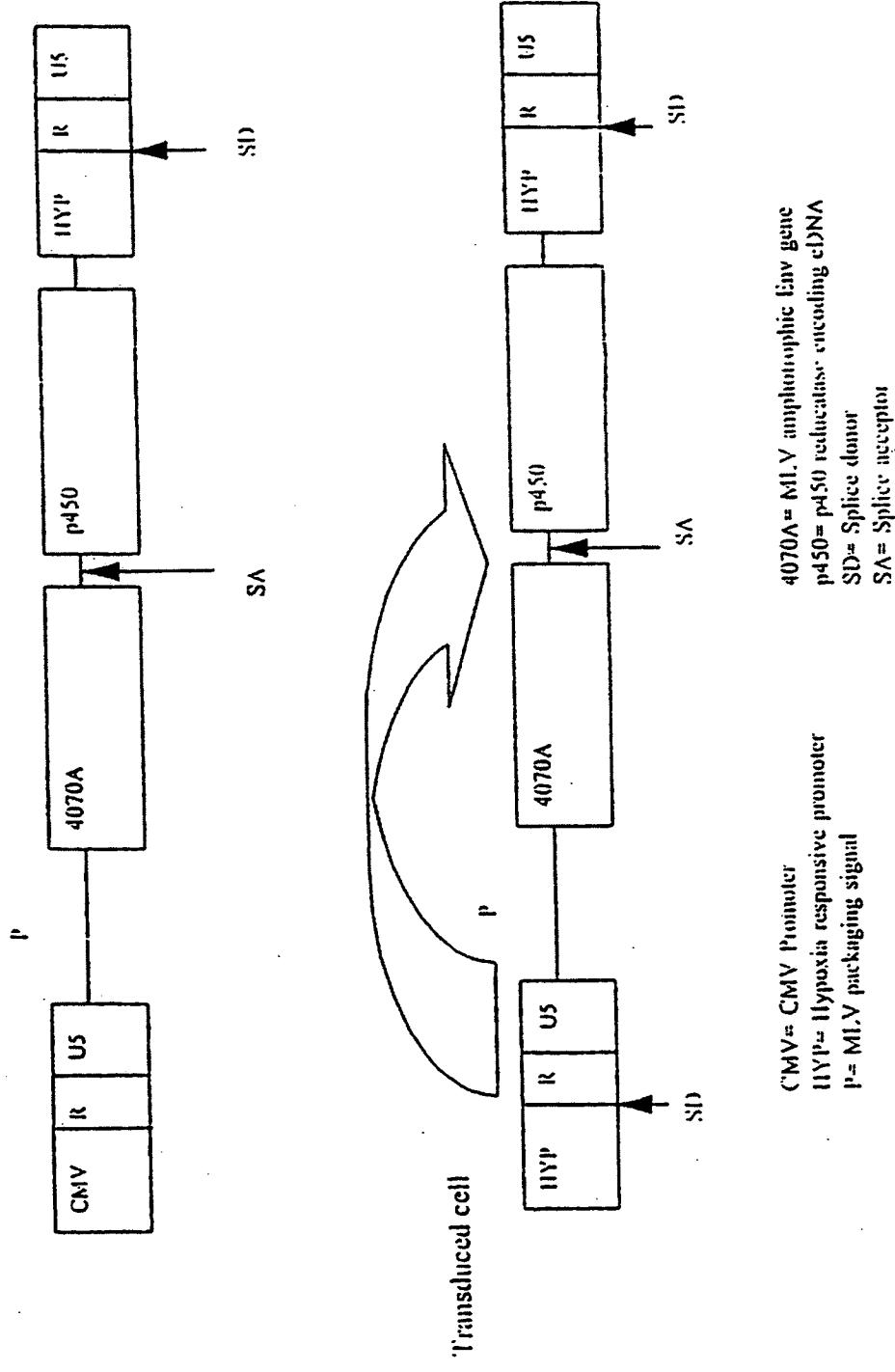




Figure 17

Packaging cell

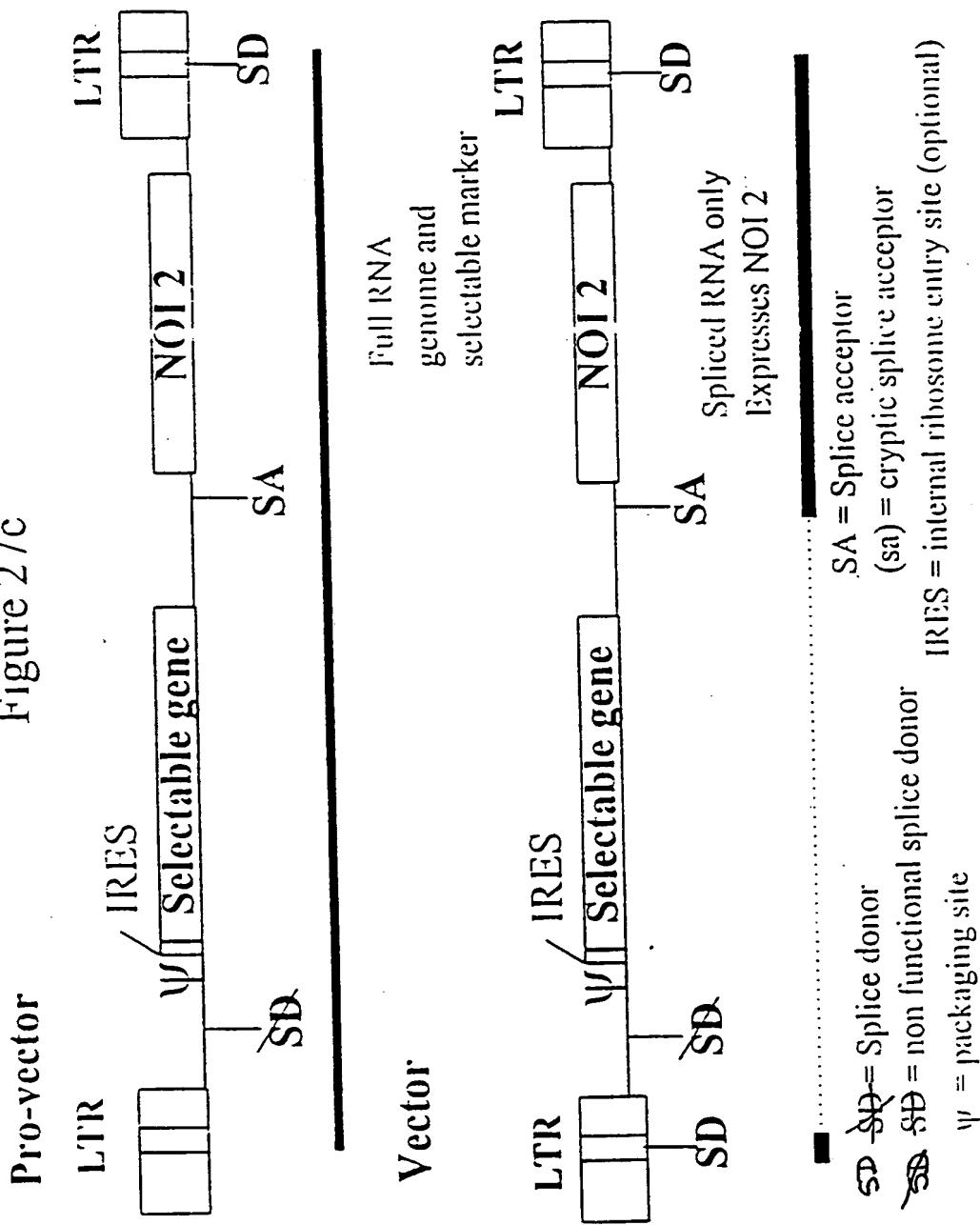


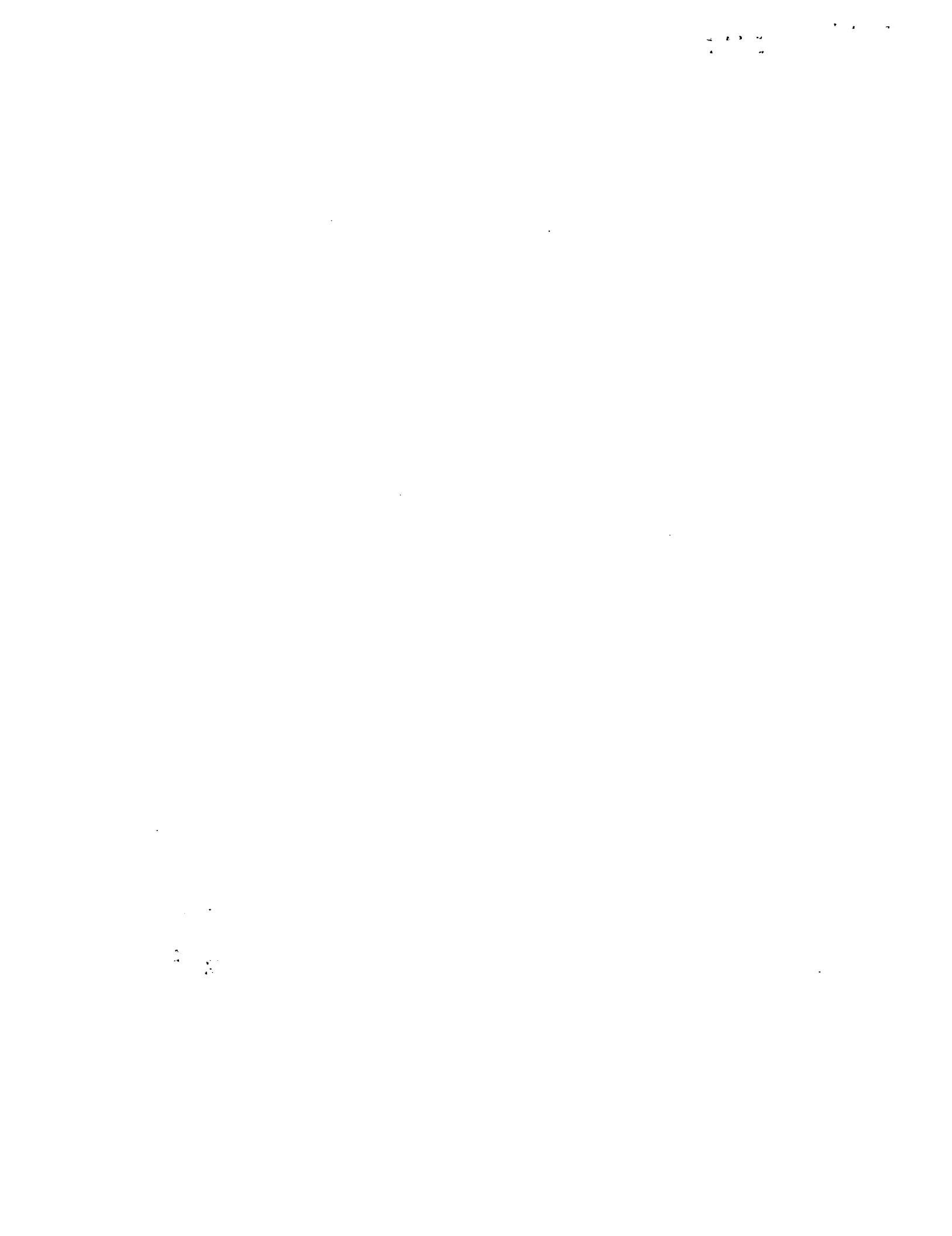
CMV = CMV Promoter
 HYP = Hypoxia responsive promoter
 P = M1.V packaging signal
 SD = Splice donor
 SA = Splice acceptor

4070A = M1.V amphotrophic Env gene
 p450 = p450 reductase encoding cDNA
 SD = Splice donor
 SA = Splice acceptor



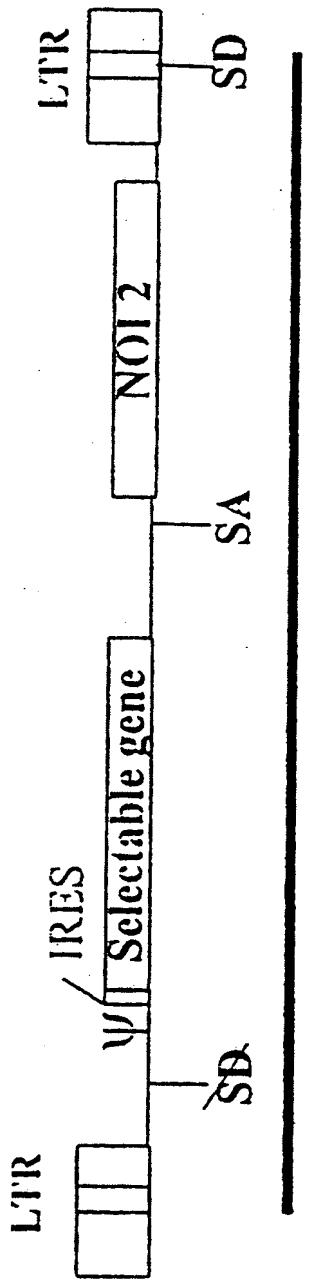
Figure 27c





Pro-vector

Figure 27c



Vector

